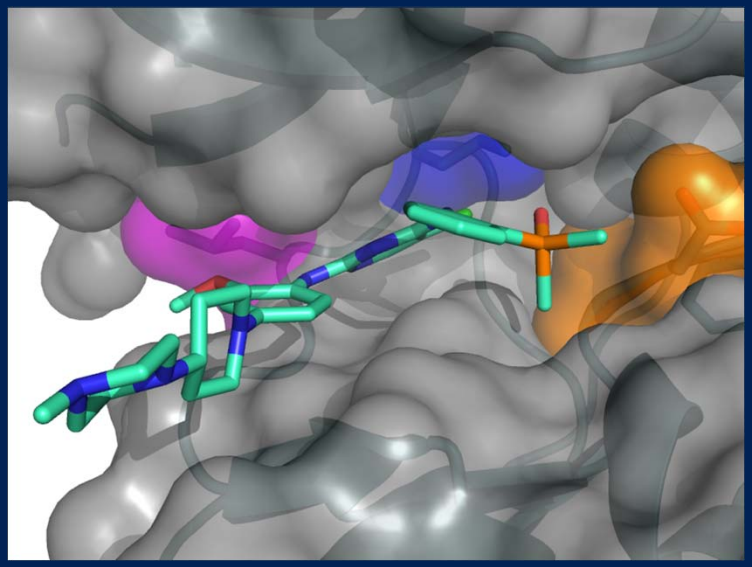
Brigatinib in Patients With Crizotinib-Refractory ALK+ Non–Small Cell Lung Cancer: First Report of Efficacy and Safety From a Pivotal Randomized Phase 2 Trial (ALTA)

Dong-Wan Kim, Marcello Tiseo, Myung-Ju Ahn, Karen L Reckamp, Karin Holmskov Hansen, Sang-We Kim, Rudolf M Huber, Howard L West, HJ Groen, Maximilian J Hochmair, Natasha B Leighl, Scott N Gettinger, Corey J Langer, Luis Paz-Ares Rodríguez, Egbert F Smit, Edward S Kim, William Reichmann, David Kerstein, Frank G Haluska, D Ross Camidge

The American Society of Clinical Oncology (ASCO) Annual Meeting, June 3–7, 2016, Chicago, IL
Abstract 9007

PRESENTED AT: ASCO ANNUAL MEETING '16

Background



Brigatinib binding ALK kinase domain[6]

- Most ALK+ NSCLC patients treated with crizotinib eventually progress, often due to acquired ALK resistance mutations and/or poor CNS drug penetration[1-2]
- With the current ALK inhibitors approved in the post-crizotinib setting, progression occurs rapidly, and secondary ALK resistance mutations have been identified[2-4]
- Brigatinib, an investigational next-generation ALK TKI, was designed to have potent and broad activity against resistant ALK mutants[5]

(1) Costa, et al. *J Clin Oncol*. 2015;33:1881-8. (2) Zhang, et al. *Lancet Oncol*. 2015;16:e510-21. (3) Ou, et al. *J Clin Oncol*. 2016;34:661-8.
(4) Mok, et al. *J Clin Oncol*. 2015;33(suppl):abstract 8059. (5) Zhang, et al. *Cancer Res*. 2015;75(15 suppl):abstract 781. (6) Source: ARIAD data on file.

Brigatinib Exhibits a Pan-Inhibitory Preclinical Profile Against ALK Resistance Mutants

- Brigatinib overcomes mechanisms of resistance to first- and second-generation ALK inhibitors in preclinical models[1]
  - Potently inhibited all ALK resistance mutations tested, including G1202R, at clinically achievable levels
  - Significantly prolonged survival and reduced tumor burden in an ALK-dependent orthotopic brain tumor model in mice
- Brigatinib yielded promising clinical activity in crizotinib-treated ALK+ NSCLC patients in a phase 1/2 study[2]

Effective Average Concentration (C_{ave}) in Patients* Exceeds IC_{50} by at Least 2-fold	Yes / No

ALK Variant	TKI Activity, IC_{50} (nM)			
	Crizotinib	Ceritinib	Alectinib	Brigatinib
Native	107	37	25	14
T1151Tins	1109†	283	201	114
L1152R	844†	437†	62	11
L1152P	721	451	48	20
C1156Y	529†	195	67	45
I1171N	532†	119	724†	124
F1174C	238	109†	31	58
F1174L	253†	117	44	55
F1174V	257†	121†	46	64
V1180L	170	16	597	11
L1196M	589†	67	133	41
L1198F	17	697	84	82
G1202R	617†	354†	695†	184
D1203N	459†	159	42	79
S1206F	199†	39	34	43
S1206Y	179†	42	19	36
E1210K	240	80	59	107
G1269A	509†	29	56	9

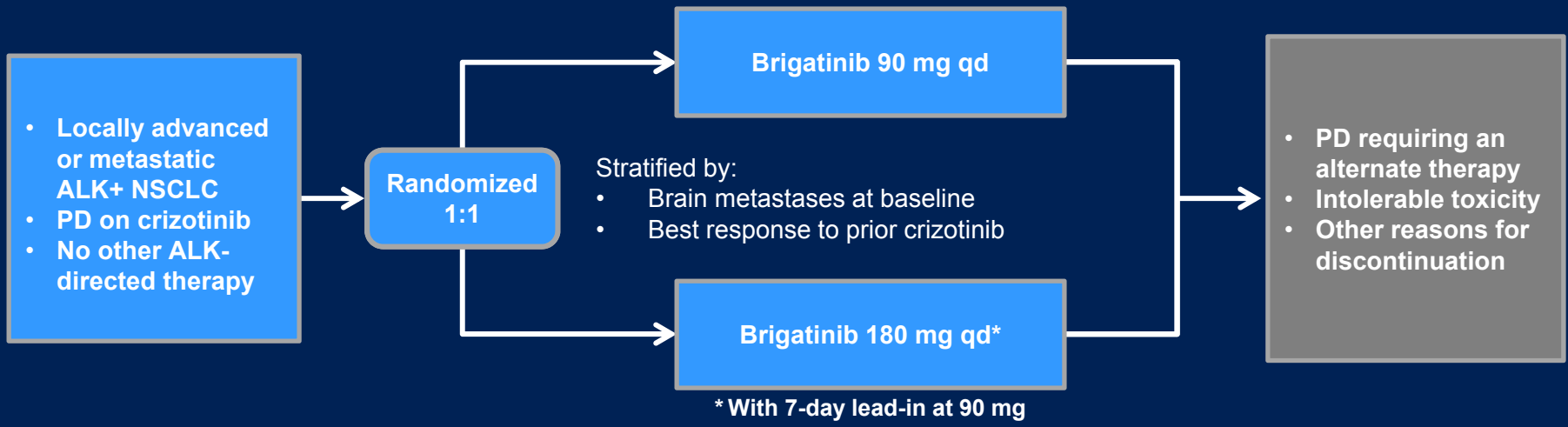
*** Effective C_{ave} at steady-state concentrations at approved/recommended phase 2 doses (180 mg for brigatinib) corrected for functional effects of protein binding; †ALK mutations previously associated with clinical resistance[3,4]**

(1) Zhang, et al. *Cancer Res*. 2015;75(15 suppl):abstract 781.
(2) Camidge, et al. *J Clin Oncol*. 2015;33(suppl):abstract 8062.
(3) Katayama, et al. *Clin Cancer Res*. 2015;21:2227-35.
(4) Friboulet, et al. *Cancer Discov*. 2014;4:662-73.

Adapted from Zhang, et al. Poster presented at AACR Annual Meeting, April 18–22, 2015, Philadelphia, PA, Abstract 781.

ALTA: Randomized Dose Evaluation of Brigatinib

A phase 2, open-label, multicenter, international study (NCT02094573)



*** With 7-day lead-in at 90 mg**

Primary Endpoint: Confirmed ORR per RECIST v1.1 (assessed by investigator)

Key Secondary Endpoints: Confirmed ORR (assessed by an IRC), CNS response (IRC-assessed intracranial ORR and PFS in patients with active brain metastases†), duration of response, PFS, OS, safety, and tolerability

Randomized phase 2 design not intended for statistical comparisons between arms; however, post hoc comparisons were performed on PFS and OS to support dose selection

† Active brain metastases were defined as lesions with no prior radiotherapy or those with investigator-assessed progression after prior radiotherapy

Key Inclusion/Exclusion Criteria and Study Status

- Key inclusion criteria
  - Adults with crizotinib-resistant ALK+ NSCLC
  - No restrictions on number of prior chemotherapy regimens
  - ECOG performance status ≤2
- Key exclusion criteria
  - Prior ALK TKI other than crizotinib
  - Crizotinib within 3 days
  - Symptomatic CNS metastases that are neurologically unstable or require an increasing dose of corticosteroids
- Data as of February 29, 2016

	90 mg qd	180 mg qd*
Randomized, n	**112**	**110**
Treated, n (%)	**109 (97)**	**110 (100)**
Remain on study, n (%)	**64 (57)**	**76 (69)**
Median follow-up, months (range)	**7.8 (0.1–16.7)**	**8.3 (0.1–20.2)**

*** 180 mg qd with 7-day lead-in at 90 mg**

Demographics and Baseline Characteristics

		90 mg qd n=112	180 mg qd* n=110	Total N=222
Median age, y (range)		50.5 (18–82)	56.5 (20–81)	54 (18–82)
Gender, n (%)	Female	62 (55)	64 (58)	126 (57)
Race, n (%)	White	72 (64)	76 (69)	148 (67)
	Asian	39 (35)	30 (27)	69 (31)
	Other	1 (1)	4 (4)	5 (2)
ECOG, n (%)	0/1	105 (94)	101 (92)	206 (93)
	2	7 (6)	9 (8)	16 (7)
Smoking history, n (%)	No	71 (63)	63 (57)	134 (60)
	Yes	40 (36)	47 (43)	87 (39)
	Unknown	1 (1)	0	1 (<1)
Histology, n (%)	Adenocarcinoma	107 (96)	108 (98)	215 (97)
	Other	5 (4)	2 (2)	7 (3)
Prior chemotherapy, n (%)	Yes	83 (74)	81 (74)	164 (74)
Brain metastases at baseline,† n (%)	Present	80 (71)	74 (67)	154 (69)
Best response to prior crizotinib, n (%)	CR or PR	71 (63)	73 (66)	144 (65)
	Other response or unknown	41 (37)	37 (34)	78 (35)

CR = complete response, PR = partial response. * 180 mg qd with 7-day lead-in at 90 mg; † Presence of brain metastases as assessed by the investigator

- Arms balanced for important prognostic factors including gender, ECOG PS (0/1 vs. 2), brain metastases, prior chemotherapy, and prior response to crizotinib

Data as of February 29, 2016

Objective Response Rates in Crizotinib-Resistant Patients by Arm

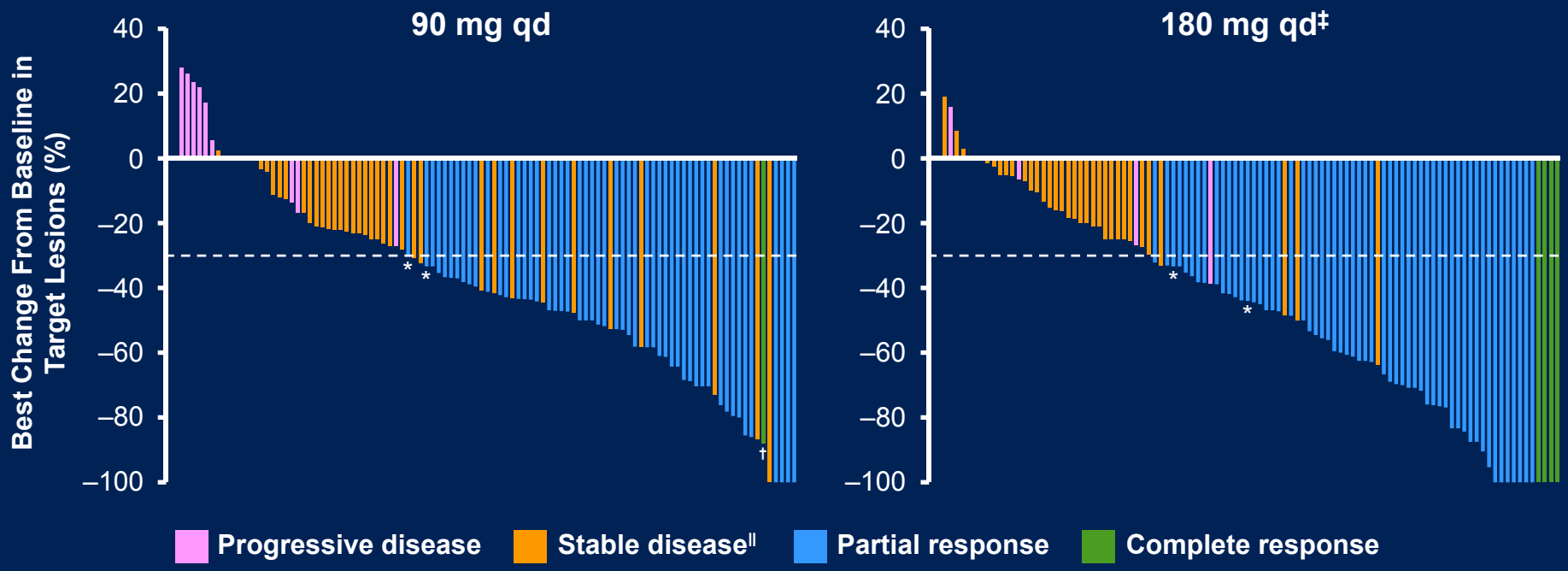
Investigator-Assessed Efficacy Parameter	90 mg qd n=112	180 mg qd* n=110
Confirmed ORR, n (%) [97.5% CI]†	50 (45) [34–56]	59 (54) [43–65]
Confirmed CR, n (%)	1 (1)	4 (4)
Confirmed PR, n (%)	49 (44)	55 (50)
PR awaiting confirmation, n (%)	2 (2)	2 (2)
Disease control rate, n (%) [95% CI]	92 (82) [74–89]	95 (86) [79–92]
Confirmed ORR by history of prior chemotherapy, n/N (%)		
Yes	35/83 (42)	44/81 (54)
No	15/29 (52)	15/29 (52)

CR = complete response, PR = partial response
* 180 mg qd with 7-day lead-in at 90 mg; † Primary endpoint tested at 0.025 level for each dose

- Responses include a confirmed PR at 180 mg in a patient with G1202R at baseline

Data as of February 29, 2016

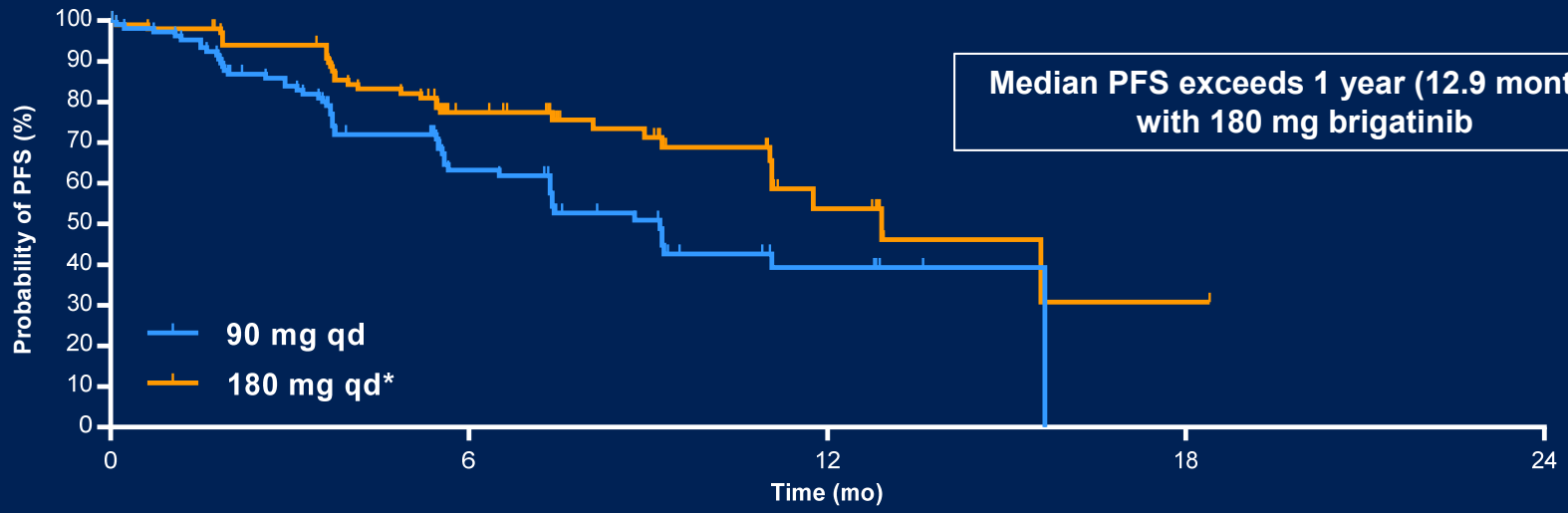
Brigatinib Antitumor Activity by Arm



Dotted line at –30% indicates threshold for partial response per RECIST v1.1
* Single response awaiting confirmation
† Patient had a lymph node target lesion which resolved to <10 mm shortest diameter (CR per RECIST v1.1)
‡ 180 mg qd with 7-day lead-in at 90 mg
‖ Category includes single responses that were not confirmed

Data as of February 29, 2016

PFS by Arm



Median PFS exceeds 1 year (12.9 months) with 180 mg brigatinib

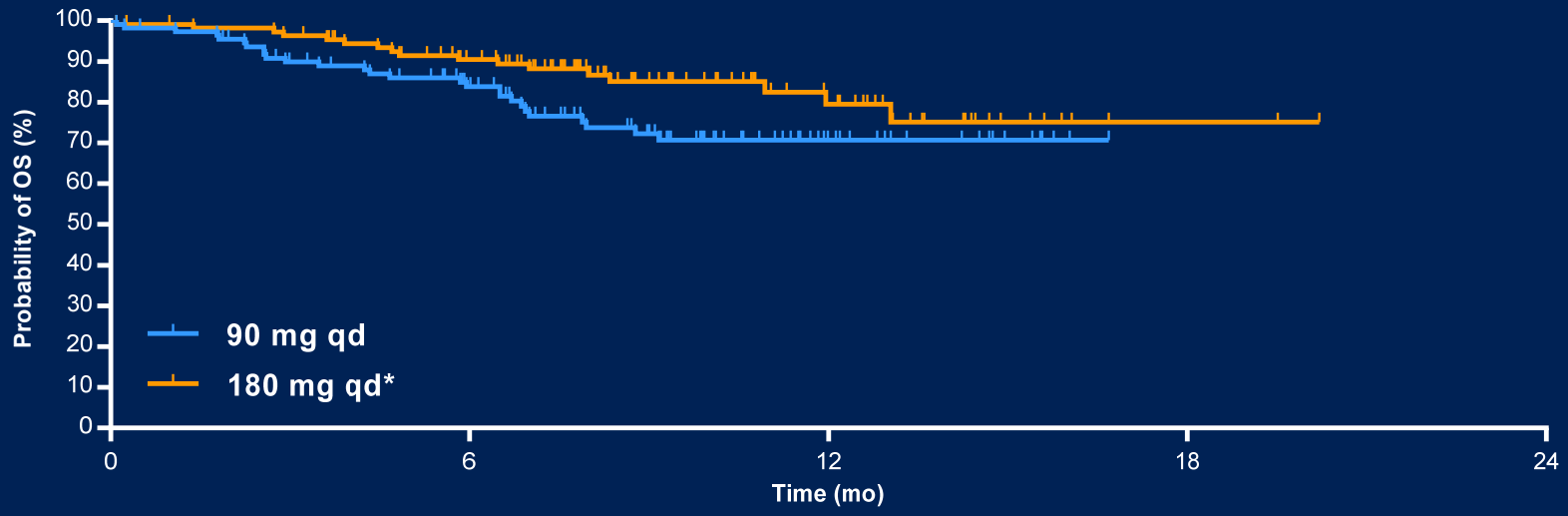
	Events / Total (%)	1-Year PFS Probability, % (95% CI)	Median PFS (95% CI)	Hazard Ratio (95% CI)†
90 mg qd	50/112 (45)	39 (27–52)	9.2 months (7.4–15.6)	0.55 (0.35–0.86)
180 mg qd*	31/110 (28)	54 (37–68)	12.9 months (11.1–not reached)	

* 180 mg qd with 7-day lead-in at 90 mg

† Study was not designed to compare treatment arms statistically; however, post hoc comparisons were performed to support dose selection

Data as of February 29, 2016

Survival by Arm



	Events / Total (%)	1-Year OS Probability, % (95% CI)	Median OS	Hazard Ratio (95% CI)†
90 mg qd	27/112 (24)	71 (60–79)	Not reached	0.57 (0.31–1.05)
180 mg qd*	17/110 (15)	80 (67–88)	Not reached	

* 180 mg qd with 7-day lead-in at 90 mg

† Study was not designed to compare treatment arms statistically; however, post hoc comparisons were performed to support dose selection

Data as of February 29, 2016

IRC-Assessed Intracranial Response Rates

IRC-Assessed Efficacy Parameter	Patients With Measurable (≥10 mm) Brain Metastases		Patients With Only Nonmeasurable Brain Metastases	
	90 mg qd n=25	180 mg qd* n=18	90 mg qd n=54	180 mg qd* n=54
Confirmed intracranial ORR, n (%) [95% CI]	9 (36) [18–58]	12 (67) [41–87]	3 (6) [1–15]	10 (19) [9–31]
Best overall response, n (%)				
Confirmed intracranial CR	2 (8)	0	3 (6)	10 (19)
Confirmed intracranial PR	7 (28)	12 (67)	NA	NA
Intracranial CR awaiting confirmation	0	0	0	1 (2)
Intracranial PR awaiting confirmation	3 (12)	0	NA	NA
Intracranial disease control rate, n (%) [95% CI]	22 (88) [69–98]	15 (83) [59–96]	39 (72) [58–84]	47 (87) [75–95]

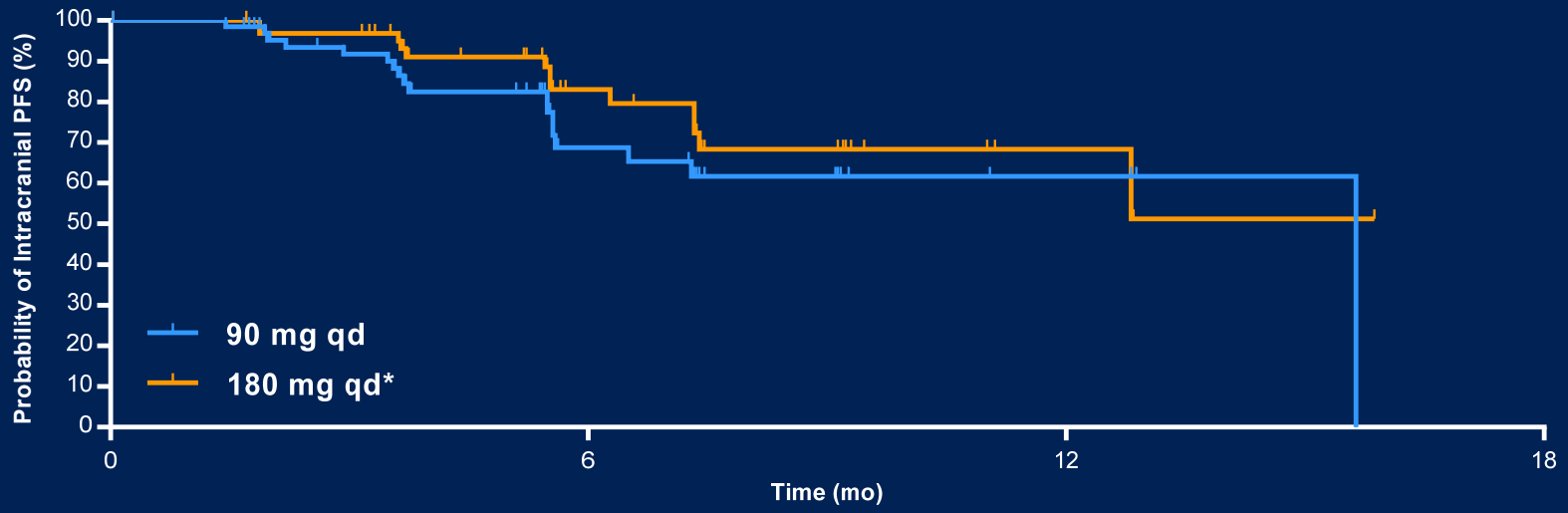
Of 222 randomized patients, 215 had a baseline brain MRI evaluated by the IRC, with 151 identified as having brain metastases at baseline
Intracranial response defined as a ≥30% decrease in measurable lesions or complete disappearance of lesions in patients with only nonmeasurable lesions
NA = not applicable

- **Among patients with measurable, active† brain metastases at baseline, IRC-assessed intracranial ORR:**
  - **37% (7/19) at 90 mg**
  - **73% (11/15) at 180 mg**

* 180 mg qd with 7-day lead-in at 90 mg
† Active brain metastases were defined as lesions with no prior radiotherapy or those with investigator-assessed progression after prior radiotherapy

Last scan date: February 17, 2016

Intracranial PFS by Arm



	Events / Total (%)	Median Intracranial PFS (95% CI)	Hazard Ratio (95% CI)†
90 mg qd	18/79 (23%)	15.6 months (6.5–15.6)	0.66 (0.32–1.35)
180 mg qd*	13/72 (18%)	Not reached (7.4–not reached)	

* 180 mg qd with 7-day lead-in at 90 mg

† Study was not designed to compare treatment arms statistically; however, post hoc comparisons were performed to support dose selection

Last scan date: February 17, 2016

Treatment-Emergent Adverse Events

Treatment-Emergent AEs Reported in ≥10% of All Patients	90 mg qd n=109		180 mg qd* n=110	
	Any Grade, %	Grade ≥3, %	Any Grade, %	Grade ≥3, %
Nausea	33	1	40	1
Diarrhea	19	0	38	0
Headache	28	0	27	1
Cough	18	0	34	0
Fatigue	20	1	27	0
Vomiting	24	2	23	0
Dyspnea	21	3	21	2
Increased blood creatine phosphokinase	11	3	30	9
Decreased appetite	22	1	15	1
Constipation	19	1	15	0
Hypertension	11	6	21	6
Muscle spasms	12	0	17	0
Arthralgia	14	1	14	0
Back pain	10	2	15	2
Abdominal pain	17	0	8	0
Rash	7	1	16	3
Increased amylase	8	1	15	1
Increased aspartate aminotransferase	8	0	15	0
Pyrexia	14	0	6	1

* 180 mg qd with 7-day lead-in at 90 mg; median time on treatment was 7.5 months in 90 mg qd arm and 7.8 months in 180 mg qd arm

- **Some AEs appear dose-related; the increased rates are mainly in grade 1–2 events**

Data as of February 29, 2016

Dose and Safety

Select Safety Parameters	90 mg qd n=109	180 mg qd* n=110
Dose reduction due to any AE, n (%)	8 (7)	22 (20)
Dose interruption ≥3 d (any reason), n (%)	20 (18)	40 (36)
Discontinuation due to any AE, n (%)	3 (3)	9 (8)
Discontinuation due to PD, n (%)	33 (30)	19 (17)
Discontinuation due to death, n (%)	7 (6)	1 (1)
Median dose intensity, mg/d	90	174

* 180 mg qd with 7-day lead-in at 90 mg

- A subset of pulmonary AEs with early onset (median: Day 2; range: Day 1–9) including dyspnea, hypoxia, cough, pneumonia, or pneumonitis occurred in 14 (6%) patients (3% with grade ≥3 events)
- All of these events occurred at 90 mg in both arms; no events with early onset occurred after escalation to 180 mg
- Managed with dose interruption and successful reintroduction (6/14) or continued treatment with resolution (1/14)
- Seven patients discontinued, including 1 patient who died having had such AEs (dyspnea, cough, and pneumonia)
  - Autopsy: lymphangitic carcinomatosis, widespread post-tumor lung scarring, and diffuse alveolar damage; causes of death reported as lung cancer, adhesive pericarditis, and respiratory failure
- Although pathophysiology is unclear, trend toward lower frequency of these AEs with ≥7-day crizotinib washout (4/110), compared with <7-day washout (10/109)
  - Relative risk: 2.52 (95% CI: 0.82–7.80)

Data as of February 29, 2016

Conclusions

- Brigatinib demonstrated substantial efficacy and an acceptable safety profile in both arms
- At 180 mg (with 7-day lead-in at 90 mg):
  - 54% ORR
  - 67% intracranial ORR (for patients with measurable brain metastases)
  - Median PFS >1 year (12.9 months); 80% 1-year OS
- Observed clinical activity at 180 mg with 7-day lead-in at 90 mg was not associated with an increased risk of additional early pulmonary AEs
- A consideration of efficacy outcomes and AEs supports choice of 180 mg regimen
- Brigatinib has the potential to be a promising new treatment option for patients with crizotinib-resistant ALK+ NSCLC
- A randomized, phase 3 study of brigatinib with 180 mg regimen vs crizotinib in ALK inhibitor–naive patients has been initiated (ALTA-1L, NCT02737501)

Acknowledgments

- We would like to thank the patients, their families, and their caregivers; the ALTA investigators and their team members at each study site; and colleagues from ARIAD Pharmaceuticals, Inc.
- Professional medical writing assistance was provided by Pamela Barendt, PhD, of Peloton Advantage, LLC, Parsippany, New Jersey, and funded by ARIAD Pharmaceuticals, Inc.